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P.O. BOX 10500 MCLEAN, VA 22102				BRANNOCK, MICHAEL T	
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				1646	

DATE MAILED: 02/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.

Applicant(s)

09/825,882

Adler et al.

Examin

Office Action Summary

Michael Brannock

Art Unit **1646**



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --Period for Reply A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION. - Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. . If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b). Status 1) X Responsive to communication(s) filed on Nov 12, 2002 2b) X This action is non-final. 2a) This action is **FINAL**. Since this application is in condition for allowance except for formal matters, prosecution as to the merits is 3) closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213. Disposition of Claims is/are pending in the application. 4) X. Claim(s) 1-137 4a) Of the above, claim(s) 23-25, 54-77, 81, 85-124, and 134-137 is/are withdrawn from consideration. is/are allowed. 5) ... Claim(s) 6) X Claim(s) 1-22, 26-53, 78-80, 82-84, and 125-133 is/are rejected. is/are objected to. 7) ...: Claim(s) are subject to restriction and/or election requirement. 8) Claims **Application Papers** 9) X The specification is objected to by the Examiner. 10) The drawing(s) filed on is/are a) accepted or b) objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). 11) The proposed drawing correction filed on ______ is: a) ____ approved_b) disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action. The oath or declaration is objected to by the Examiner. Priority under 35 U.S.C. §§ 119 and 120 Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). 13). a) All b) Some* c) None of: 1. Certified copies of the priority documents have been received. Certified copies of the priority documents have been received in Application No. 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). *See the attached detailed Office action for a list of the certified copies not received. 14) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). The translation of the foreign language provisional application has been received. 15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121. 1) X Notice of References Cited (PTO-892) Interview Summary (PTO-413) Paper No(s). Notice of Draftsperson's Patent Drawing Review (PTO-948) Notice of Informal Patent Application (PTO-152) Information Disclosure Statement(s) (PTO-1449) Paper Nois).

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DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 1-137 are pending.

2. Claims 23-25, 54-77, 81, 85-124 and 134-137 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10, 8/2/02 and in Paper No. 12, 11/21/02.

Applicant's election with traverse of Group I, as the claims relate to SEQ ID NO: 7/8, in Paper 10 is acknowledged. In Paper 12, Applicant asserts that claims 1-22, 26-53, 78-80, 82-84, 125-133 read on the elected invention. Applicant asserts that the DNAs in this application encode structurally and functionally related human T2R species that are all involved in bitter taste sensation; and that therefore, upon determination that the elected species is allowable, Applicant requests that the search be extend to other T2R nucleic acid sequences. This is not found persuasive for the following reasons. Each of the recited sequences represent a structurally and presumably functionally distinct molecule, the use of one not being required for the use of any other. Even what could be termed a singular modality of taste perception, e.g. the perception of bitter taste, is known to involve multiple and as yet poorly characterized transduction schemes, see for example Perruccio and Kleinhaus, *Society for Neuroscience Abstracts* 26(1-2) Abstract No. 66.15, 2000. Thus, the various receptors would be expected to be functionally divergent; they are also clearly structurally divergent and distinct, as evidenced by the differences in the

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primary amino acid sequences. Although a search of one SEQ ID NO may overlap that of another, no two searches would be coextensive, and nor could one search be relied upon to provide art that is anticipatory or might render obvious any other SEQ ID NO; and to search all species in a single application would be unduly burdensome. Thus, the molecules represented by the different SEQ ID NOs represent patently distinct inventions. Therefore, the restriction requirement is maintained and made final.

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-22, 26-53, 78-80, 82-84, 125-133 of this application. The prior application does not appear to disclose a polynucleotide corresponding to the instant SEQ ID NO: 7 or encoding a polypeptide of the instant SEQ ID NO: 8.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink(s) and/or other form of browser-executable code, see page 17 for example. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

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Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 26-38, 47-53, 78-80, 82 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons.

Claims 1 and 27, require a "variant" of a DNA. The word "variant" is used in the art to denote a relative relationship between two things, yet the specification has not set forth a clear distinction between what is to be considered a "variant" and what is considered to be unrelated. Thus, the artisan could not unambiguously know whether or not he or she was in possession of polynucleotides that are encompassed by Applicant's claims.

Claim 1 and dependent claims 36-53, 78-80, 82 and 83 require that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. The term appears to be defined only by way of example at page 31. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, e.g., salt concentration and temperature conditions of incubations and washes.

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Claims 2, 3, 4, 27 and 38 recite the phrase "or a fragment thereof". Because of the sentence structures of the claims, it is impossible to determine what part of the claims the phrase is in reference to, e.g. in claim 2 it is unclear if the phrase relates to the "isolated nucleic acid molecule of claim 1" or to "isolated nucleic acid molecule of claim 1 which is selected from the group consisting of SEQ ID NOs: 1, 3, 5 etc". Such a distinction would determine the bounds of the claim.

Claims 26-35 and 78-80 require a nucleic acid molecule that is indirectly attached to a nucleic acid sequence. The specification has not set forth a qualitative definition as to what constitutes an "indirect" attachment, and nor has the specification set forth a quantitative standard such that the artisan could measure the degree of directness so as to determine if something was indirectly attached. Therefore the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

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8. Claims 1-22, 26-53, 78-80, 82-84, 125-133 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The claims are directed to polynucleotides of SEQ ID NO: 7 encoding a polypeptide of SEQ ID NO: 8 termed hT2R61, wherein the polypeptide is believed to be a component of a taste transduction pathway, particularly bitter taste transduction (page 8). The specification puts forth the instant hT2R61 is a member of the T2R family of taste-cell-specific GPCRs as described in Chandrashekar et al., Cell 100(703-711)2000; and that such family members are believed to involved in the taste detection of bitter substances but may be involved in other taste modalities as well, (see page 8, last full paragraph). The instant specification puts forth that the polypeptides are useful for "representing the perception of taste and/or for predicting the perception of taste in a mammal" (e.g. pg 67), although the specification does not appear to assert that the instant polypeptide mediates a response to any particular tastant or ligand. The specification suggests that the nucleic acids and the proteins they encode can be used as probes to dissect taste-induced behaviors (e.g. see page 6). Further, the specification indicates that the polypeptides can be used in a screening method to determine what molecules may activate or inhibit the polypeptides (see pages 9 and 50) and also to determine what the physiological effects of the polypeptides might be - the effects being those on "taste modulation". These proposed uses lack a substantial utility, because each of the proposed uses are of a general nature, and it would require undue experimentation on the part of the skilled artisan to determine what, particularly, the claimed polynucleotides could be used for.

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A substantial utility is a practical use which amounts to more than a starting point for further research and investigation and does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. For example, an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease would be a practical use of the material. However, a method of modulating an unidentified aspect of what is collectively known as taste perception with an as yet unidentified material (e.g. agonists of the disclosed polypeptides) would not constitute a substantial utility. Basic research, such as studying the properties of the claimed product or the mechanisms in which the product is involved, does not constitute a substantial utility.

A stated belief that a correlation exists between the polypeptides and any of the collective phenomena that are encompassed by the concept of taste perception is not sufficient guidance to use the claimed polynucleotides to modulate any aspect of taste perception; it merely defines a starting point for further research and investigation and presents only an invitation to one of skill in the art to perform such further research and investigation. The molecular mechanisms of taste perception are extremely complex and are known to use multiple transduction mechanisms. Even what could be termed a singular modality of taste perception, e.g. the perception of bitter taste, is known to involve multiple and as yet poorly characterized transduction schemes, see for example Perruccio and Kleinhaus, *Society for Neuroscience Abstracts* 26(1-2) Abstract No. 66.15, 2000. Thus, Applicants' asserted uses of the polynucleotides as they relate to taste perception, are general and do not assert any particular use

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beyond an invitation to the skilled artisan to try to find a particular way in which the polynucleotides or polypeptides could be used.

Further, the asserted membership of the instant polypeptide in the family of T2R proteins described by Chandrashekar et al., (supra) does not, alone, impart a property to the polypeptide that could be exploited in such a way as to constitute a substantial utility. Chandrashekar et al. tested 11 different human T2R clones against a battery of different tastants and found only one clone that responded - and this response seems to be limited to only one tastant (see col 1 of page 707 and List of Tastants at page 710). Further, even this success seems to be rare in the art. Commenting on this family of receptors, other researchers have concluded that although T2R receptors have been suggested to be candidates for bitter taste receptors, "at present there is no functional evidence for this proposal", see Lindemann, B. *Nature Neuroscience* 3(2)99-100, 2000, last paragraph of column 2 of page 99. Applicant's disclosure simply offers an additional object for the skilled artisan to examine. Although Applicant's disclosure would be immediately recognized as presenting an exciting research opportunity, a product whose only asserted utility is as an object of such research is not patentable under 35 U.S.C. 101.

The specification puts forth that the polypeptides of the instant invention are specifically expressed in taste cells and that the polynucleotides could thus be used to generate taste topographic maps or to dissect taste transduction pathways (e.g. page 68-70). These proposed uses lack a substantial utility. Almost every polynucleotide and polypeptide has some tissue specific pattern of expression, and absent knowledge of any ligands to the disclosed

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polypeptides, or without some specific or particular guidance as to which "taste transduction pathway" the polypeptides are involved in, these uses are merely and invitation to perform further research into the properties of the disclosed polypeptides and polynucleotides or to try to find practical uses for them.

The specification puts forth that the polypeptide and/or polynucleotides could be used in forensic biology (page 69). While one of skill in the art would appreciate that polymorphisms in the disclosed sequences must exist in any large population, this amounts to nothing more than an invitation to the skilled artisan to try and find such polypmorphisms. Moreover, the specification does not teach that any particular nucleic acid or amino acid sequence is distinctive of any individual nor of any particular phenotype.

Thus, the instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids.

9. Claims 1-22, 26-53, 78-80, 82-84, 125-133 are also rejected under 35 U.S.C. § 112 first paragraph. Specifically, since the claimed invention is not supported by a substantial asserted utility, for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

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Additionally, should Applicant establish a substantial utility for the claimed polynucleotides, claims 1-22, 26-45, 47-53, 78-80, 82-84, 125-133 encompass polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 8 i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 8 or comprising only portions of SEQ ID NO: 8 Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 8, but which still retain a desired property of the polypeptide of SEQ ID NO: 8.

The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 8 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 8 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 8, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 8.

The specification has failed to provide an activity of SEQ ID NO: 8 to be used to evaluate the claimed variants for usefulness. The specification has not provided a working example of a

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usable variant of the polypeptide of SEQ ID NO: 8 nor sufficient guidance so as to enable one of skill in the art to make such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy

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the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 8 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants (e.g. pages 26-28), this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The problem of producing active variants appears especially difficult in the art of T2R receptors, to which the instant polypeptide is asserted to belong. The instant specification appears to simply suggest to the artisan that art-recognized procedures for screening GPCRs (e.g. pages 50-63) are sufficient to identify functional variants of SEQ ID NO: 8 However, Hoon *et al.*, *Cell* 96(541-551)1999, report that "We have attempted to determine the ligand/tastant specificity of TR1 and TR2 using a variety of strategies but have been hampered by the difficulty of functionally expressing these molecules in heterologous systems" see col 1 of page 547.

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Further, Chandrashekar et al. reported that they were able to record a response from only 1 of the 11 human T2R clones tested, see col 1 of page 707, and see above. Thus, the art regarding T2R receptors, as exemplified by Hoon et al., Chandrashekar et al, and Lindemann (discussed above), recognizes the complexity, unpredictability, and non-routine nature of the work involved in trying to assay functional T2R receptors. The instant specification has provided only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such a screening method.

The specification has also failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 7, e.g. no disorder or phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might now where to obtain a variant. The specification merely offers the skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations.

Due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the difficulties encountered in screening T2Rs, exemplified by Hoon et al., Chandrashekar et al., and Lindemann, and the breadth of the claims which fail to

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recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

10. Claims 1-22, 26-45, 47-53, 78-80, 82-84, 125-133 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a cDNA polynucleotide of SEQ ID NO: 7, yet the claims encompass polynucleotides not described in the specification, e.g. mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 7, encoding a polypeptide with no instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co.* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A

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description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 7, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

The specification has not provided a particular essential feature, either a functional or structural feature, that the claimed genus of polynucleotides possess. The recitation of the property of hybridization does not, alone, provide sufficient information regarding the structure of the claimed polynucleotide variants. Further, most of these variants are expected to encode polypeptides having an amino acid sequence different than that of SEQ ID NO: 8 and thus having different structural and functional properties. Similarly, the recitation of a percent identity to SEQ ID NO: 8 provides no description of any amino acid sequence other that of SEQ ID NO: 8. The specification has not defined what particular common structural or functional properties are possessed by the claimed genus of polynucleotides. Thus one of skill in the art would appreciate that Applicant was not in possession of the claimed genus of polynucleotides at the time of filing.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 7 and has the function of the parent polynucleotide. Thus, with the exception of the of the polynucleotide of SEQ ID NO: 7, and other polynucleotides which encode a polypeptide of SEQ ID NO: 8, the skilled artisan cannot

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envision encompassed variants. Therefore, only a polynucleotides encoding a polypeptide of SEQ ID NO: 8, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- 12. Claims 1-8, 14-22, 26, 36, 37, 47-53, 78-80, 82-84, 125-133 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/42470, clone pt127_1, published August 26, 1999.

WO 99/42470 clone pt127_1 is a cDNA molecule that is 100% identical to the instant SEQ ID NO: 7 over a region of greater than 150 base pairs (see attached sequence alignment), and would thus be expected to hybridize under conditions described in the specification as highly stringent, absent evidence to the contrary. Further, WO 99/42470 clone pt127_1, encodes a polypeptide that is 62% identical to SEQ ID NO: 8 and comprises at least 25 contiguous amino

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acids of SEQ ID NO: 8 (see attached sequence alignment). WO 99/42470 teach that the encoded

protein has a leader sequence directly attached which should target the protein to the plasma

membrane (see page 44). Vectors, host cells, and methods of producing the protein are provided

(see pages 55-57 for example).

Conclusion

No claims are allowable

Any inquiry concerning this communication or earlier communications from the examiner

should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The

examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m.

The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal

communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding

should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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February 20, 2003

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